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Title Page – Detection and Prevention of Adverse Drug Reactions in Multi-Morbid Older Patients

Title: Detection and Prevention of Adverse Drug Reactions in Multi-Morbid Older Patients

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Abstract:

Adverse drug reactions [ADR] are a recognised unintentional form of iatrogenic harm, which commonly occur in older adults who have high levels of co-morbidity and polypharmacy. Research estimates that at least one in ten hospitalised older patients will experience an ADR. While recent research indicates this could be as high as 39% in hospitalised multi-morbid, older adults. Up to two thirds of these ADRs can be considered preventable and therefore, are potentially avoidable. In addition to affecting patient morbidity and contributing to avoidable mortality, there is an associated cost implication with ADR occurrence. This commentary aims to summarise current research in terms of ADR detection, prediction and prevention in multi-morbid older patients. At present, the largest barrier to understanding and comparing ADRs in the literature is the large heterogeneity that exists in the population and study methods. In addition, there is the lack of a standardised universally accepted methodology for ADR prediction, detection, causality assessment and subsequent prevention.

Methods of ADR prediction in a heterogeneous multi-morbid population to date are poor. Without an instrument that consistently and reliably predict ADR risk in a reproducible manner, ADR prevention is challenging. Further attention should be placed on the culprit drugs that lead to ADRs in older hospitalised patients with concurrent multi-morbidity and polypharmacy. The risk associated with certain drug groups may in fact be a better predictor of ADR risk than patient factors in isolation. Current research is examining this drug/drug focus on ADR prevention in multi-morbid older people.

Commentary:

At least one-in-ten older adults experience an adverse drug reaction [ADR] that directly contributes to, or occurs during their hospitalisation [1]. Beijer *et al.* indicate that for those aged 65 years and over, one in six patients (16.8%) were hospitalised due to ADR-related problems [2]. Multi-morbidity, associated polypharmacy, female sex and increased age are associated with an increased risk of ADRs [1]. ADR occurrence rates are up to twice as high in those over 65 years when compared to that of their younger counterparts [2]. Studies aimed at development of risk prediction models for ADRs in multi-morbid older adults indicate that in the acute hospital setting ADR incidence varies widely between 6.5% and 39% for this particular population [3-8]. Lazarou *et al.* [9] have extrapolated from large-scale population data that fatal ADRs in US hospitals are between the fourth and sixth leading cause of death. They reported overall fatal ADRs incidence of 0.32%, with fatal ADRs being more likely to occur during hospitalisation versus those leading to hospitalisation, 0.19% versus 0.13% [9]. A recent systematic review indicates an alarmingly higher percentage of fatal ADRs i.e. 2.69%, while preventable ADRs accounted for over half of these fatalities i.e. 1.58% [10]. As well as effects on morbidity and mortality, ADRs are highly costly. Beijer *et al.* calculated in 2002 that approximately 76,800 elderly people experience an avoidable admission in the Netherlands each year, at the cost of €2128 per admission, resulting from preventable ADRs [2]. Given the increasing older patient

population and rising longevity, ADRs and their consequences will be even more of an issue in the near future.

The level of perceived preventability of ADRs among older people in the literature is notable and suggests the need for clinicians to focus more attention on potentially avoidable negative outcomes from medication. The unacceptably high incidence of ADRs in older adults necessitates a change in ADR detection and prediction to improve practice and patient care. In studies including older adults, two-in-three hospitalisations due to ADRs are considered preventable [10]. ADR verification is often a complex process, not least because ADRs are difficult to predict reliably. Significant heterogeneity is reported regularly in systematic reviews that attempt to explore this topic. Heterogeneity is not only limited to the patient population included in these studies, but also occurs in the various methods utilized to define ADRs. The methods of ADR identification in the literature are also complex and ambiguous in many cases. ADR focused systematic reviews consistently report heterogeneity in ADR identification methods in the included studies' design. For example, in a recent systematic review, only one of fourteen studies described explicit details regarding criteria for ADR screening [1]. Furthermore, in the systematic review by Stevenson et al. [6], four different methods were used to predict ADRs in older people among the included studies. In addition to the lack of a defined robust method to identify ADR occurrence, a widely accepted method for assessing ADR causality is lacking. There are at least 34 known methods to assess ADR causality [11] and inter-rater reliability amongst these methods is not robust. Not surprisingly, no ADR causality method has been universally accepted in research or clinical practice. It appears unlikely that a highly reproducible and reliable standardised ADR causality system will emerge, given the lack of such a system to date [11].

Research in this area needs to focus on improving prediction of ADRs in older people as a means of ADR prevention. Lavan *et al.* outlined the numerous risk prediction tools reported in the literature. They concluded that with the complex nature of ADR criteria sets and the inherent difficulties with applying them to everyday practice, they are not applicable in everyday clinical practice [12]. In their systematic review, Stevenson et al. focused on four studies looking at ADR risk-prediction models for use specifically in older-patients [6]. They concluded that overall ADR prediction model performance was modest at best (area under the receiver operator curve ranging from 0.623 to 0.73), and that current models are not suitable for use in clinical practice [6]. One such model, GerontoNet ADR risk score [13], had the largest sample size [n =5963], a high level of multi-morbid illness, concurrent polypharmacy and a mean age of 78 years. It involved a representative sample of multi-morbid older patients encountered in routine clinical practice. The GerontoNet ADR risk scale would, it was proposed, allow for practical and simple identification of older patients at increased risk of ADRs. However, in a prospective study by O'Connor *et al* [5], the predictive power of the tool was subsequently shown to be weaker than that initially reported. Subsequent ADR prediction tools also proved disappointing, including the recently published ADRROP prediction scale which also fails to predict ADRs to a high level in hospitalized older adults with multi-morbidity [4]. **Table 1** outlines a direct comparison of studies exploring the development of ADR prediction models in older people. It illustrates a direct comparison of the patient population demographics included in these studies with specific emphasis on patient age, polypharmacy and multi-morbidity. In each of the included studies, patients were older, had concurrent polypharmacy and in the majority had multi-morbid illness. Despite these various attempts to derive clinically relevant ADR prediction tools involving a variety of ADR risk variables, ultimately the AUROC values are insufficient to make them clinically useful i.e. less than 0.80 for all tools, indicating that each tool's accuracy is insufficient for clinical application.

Up to now, the majority of ADR risk prediction tools have focused primarily on individual patient factors as predictive variables [**Table 1**]. However, with firm evidence showing that this approach is insufficient for predicting ADRs in elderly multi-morbid patients [3-8, 13], there is a clear-cut need for a different method that can predict, screen for and ultimately reduce ADR occurrence in multi-morbid older adults. Despite over six decades of research on ADR detection and prediction, reliable and user-friendly ADR detection and prediction methods remain stubbornly elusive. New methods of ADR prediction and detection will likely involve a shift of focus. From patient characteristics alone, to the ADR risk associated with particular drugs, drug classes, or clinical syndromes. The presence of a high-risk drug may be a better predictor of potential ADR occurrence than patient characteristics in isolation.

Despite preventative strategies described in the literature, there is little point in detecting and predicting ADRs if interventions to counteract them are lacking. Prudent goal focused prescribing, appropriate de-prescribing and medication review/optimisation appear to be the best interventions to address this challenge [12]. A recent meta-analysis of 15 interventions to reduce ADRs in older adults showed that interventions to optimize medication use were associated with lower risk of ADRs (OR 0.79, 95% CI 0.62-0.99) and fewer serious ADRs (OR 0.64, 95% CI 0.42-0.98) [14]. The causative relationship between certain medications and ADRs in older-adults is previously well-described [12]. Yet, the majority of systematic reviews only report particular culprit drugs within their defined study. The recent systematic review by Howard *et al.* examined which drugs cause preventable hospital admissions [15]. Only nine of the thirteen included papers reported on associated ADR-inducing medications, indicating that four drug classes (diuretics, NSAIDs, anti-platelet agents, anticoagulants) accounted for more than 50% of preventable ADR-related admissions, and 12 drug groups accounted for 80% of such admissions. It is unclear if these findings are directly applicable to older patients as only four of the thirteen studies included adults over 65 years. It is also likely that because of changes

in pharmaceutical products the list of drugs/drug classes will likely be different in 2018. Alhawassi *et al*. [1] reported a substantial variability across the studies that reported medications implicated in ADRs. To date, there is no systematic review specifically examining culprit drugs causing ADRs and related outcomes in hospitalised multi-morbid older adults. This is curious given that this is the most vulnerable patient population in terms of clinically serious ADRs.

The propensity for ADRs in multi-morbid older adults points to a contemporary new geriatric giant. The numbers of older multi-morbid people exposed to polypharmacy presenting to acute geriatric services are increasing, and consequently ADRs will likely increase in tandem. Research to date indicates that most ADRs are preventable, indicating that clinicians can reduce iatrogenic harm. However, methodologies developed so far for prediction and prevention of ADRs are inadequate. The onus lies with clinicians to address this growing public health problem. Those trained in geriatric medicine have a skillset that facilitates ADR prediction and reduction. However, most prescribers lack training in geriatric medicine. Most do not receive dedicated training in geriatric pharmacotherapy at an undergraduate or postgraduate level. Hence, there is a need for a new approach to ADR prediction and prevention. While there is wide heterogeneity in the patients experiencing ADRs and in the methods used to identify ADRs, a new focus on high-risk drug and drug classes alongside accurate description of patients' multi-morbidity is necessary. Such a shift in focus may be the key to improving ADR detection and prediction in multi-morbid older people.

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